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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-165

Statistical Review(s)

Statistical Review and Evaluation
Clinical Studies

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NDA #: 21-165/Class 1-S
Applicant: Schering Corporation
Name of Drug: Desloratadine 5 mg Tablets
Indication: Seasonal Allergic Rhinitis in Adults and Adolescents
Documents Reviewed: Volumes 1.1, 1.142-1.162 and data dated October 20, 1999

This review pertains to the evaluation of one Phase II dose-ranging study and 3 Phase III studies in patients with seasonal allergic rhinitis. The four onset-of-action studies included in the submission are not included in this review. One of these studies was an in-the-park study that failed to show differences from placebo. The other three were chamber studies. Chamber studies may be supportive, but do not provide sufficient evidence for a labeling claim.

The medical officer for this submission is R. Nicklas, M.D. (HFD-570), with whom this review was discussed.

I. Background

Desloratadine is the major active metabolite of loratadine, marketed in the U.S. as Claritin. Desloratadine will be denoted as DCL throughout this review.

This review will only focus on the variables Total AM/PM Symptom Score (reflective), Total Nasal AM/PM Symptom Score (reflective) and Total AM (now) Symptom Score. The first variable is the sponsor's primary efficacy variable; the second variable is most often used as the primary efficacy variable in submissions to the FDA for this indication; and the third variable, an end of dosing interval assessment, addresses the issue whether Desloratadine is an effective QD dosing regimen.

The sponsor claims in the proposed label that instantaneous assessments of efficacy at the end of the dosing interval demonstrated that reductions in symptoms were observed following the first dose of desloratadine 5 mg, and were maintained for the full 24 hour dosing interval. This reviewer will discuss whether this claim is supported by the early daily assessments in the Phase III studies using Total AM/PM Symptom Score (reflective) and Total AM Symptom Score (now).

Keywords: Clinical Studies, NDA review

II. Dose-Ranging Study (C98-001)

A. Study Description and Method of Analyses

This was a multicenter, parallel group, randomized, double-blind study with a 3 to 7 day run-in period and a two-week treatment period comparing DCL 2.5 mg, 5 mg, 7.5 mg, 10 mg, 20 mg, and placebo, all given QD in the AM, in adult and adolescent patients with seasonal allergic rhinitis.

The patients kept a daily diary in which they rated their symptoms (rhinorrhea, nasal stuffiness, nasal itching, sneezing, itching/burning eyes, tearing/watering eyes, redness of eyes, itching of ears or palate) using a 4 point scale: (0=none, 1=mild, 2=moderate, 3=severe). The first 4 symptom scores were summed and denoted by Nasal Symptom Score, the other 4 symptom scores were summed and denoted as Non-nasal Symptom Score. All 8 symptom scores were also summed to create a Total Symptom Score. The patient at arising in the AM, before taking his treatment tablet, recorded the severity of the symptoms both as a reflective rating of the last 12 hours and as a instantaneous (now) rating. Similar ratings were taken in the evening (PM ratings) at bedtime.

To enter the study, the patient had to have, at the screening visit and the baseline visit, the ~~following reflective (prior 12 hours) sign/symptom scores, as assessed~~ jointly by the investigator and patient:

1. A Nasal Rhinorrhea Symptom Score of at least 2 (moderate).
2. A Total Nasal Symptom Score of at least 6.
3. A Total Non-nasal Symptom Score of at least 5.

Since the AM score on the day of randomization was assessed before taking treatment, it represents a run-in score. If we denote the day of randomization as Day 1, then the following values were used to calculate baseline averages: AM averages were Days -2, -1, 0, and Day 1. PM averages were Days -2, -1, and 0. AM/ PM combined were averages of AM Days -2, -1, 0 and 1, and PM Days -2, -1, and 0. [Note that the protocol stated that all of the run-in data (3 to 7 days) would be used to calculate the baseline.]

The sponsor formed the following on-treatment averages for each sign/symptom and for Total Nasal Symptom Score, Total Non-nasal Symptom Score, and Total Symptom Score: AM averages of Days 2 through 15, PM averages of Days 1-15, AM/PM combined averages of Days 2 through 15. (Note that Day 1 PM scores are not included in the AM/PM combined average. The protocol did not specify how the two-week period would be calculated.)

The primary efficacy variable is change from baseline in Total AM/PM combined reflective score averaged over Days 2-15. This was analyzed by an analysis of variance with factors: treatments and centers. The sponsor first tested the 10mg dose of DCL against placebo. If this was significant, then all other doses were compared with placebo at the 0.05 level. [This method of controlling the per-experiment error rate was specified in the protocol.]

The study's planned sample size was 900 patients (150 per treatment). This sample size allowed 90% power at the 0.05 significance level to detect a 1.6 unit difference in mean changes from baseline in Total AM/PM Symptom Score between two treatment groups, assuming a pooled standard deviation of 4.5.

The primary population was a modified "intent-to-treat" population, which was defined to be patients having both baseline and on-treatment diary data.

B. Results

There were 1036 patients (173 for DCL 2.5 mg, 172 for DCL 5.0 mg, 173 for DCL 7.5 mg, 172 for DCL 10mg, 172 for DCL 20 mg, and 174 placebo) randomized at 29 centers. A total of 58 patients (11 DCL 2.5 mg, 12 DCL 5.0 mg, 9 DCL 7.5 mg, 9 DCL 10 mg, 8 DCL 20 mg, and 9 placebo) failed to complete the study. Of these, 20 were for treatment failure (5 DCL 2.5 mg, 3 DCL 5.0 mg, 2 DCL 7.5 mg, 2 DCL 10 mg, 2 DCL 20 mg, and 6 placebo).

The treatment groups were comparable in demographic and baseline symptom severity.

Ten subjects were not included in the intent-to-treat analysis of the primary efficacy variable because they failed to have both baseline and on-treatment diary assessments.

Table 1 provides the results of the analyses of Total Symptom Score (reflective) for combined AM/PM averages over Days 2-15, Total Nasal Symptom Score (reflective) for combined AM/PM averages over Days 2-15, and Total Symptom Score AM (instantaneous assessment) averages over Days 2-15. The 2.5 mg dose of DCL failed to show efficacy over placebo, whereas all the other doses showed efficacy. Because the sponsor saw little difference between these 5 mg to 20 mg doses, the sponsor chose to use the 5 mg and 7.5 mg dose in the Phase III trials.

Significance from placebo was seen in Total Symptom Score (both AM/PM reflective and AM instantaneous) on Day 2 for all treatment doses except the 2.5 mg dose of DCL. The 5 mg dose of DCL was not significantly different from placebo at Day 3 ($p=0.10$) but was significant at Day 4 for Total AM Symptom Score (instantaneous). The higher doses showed significant differences at Days 2, 3, and 4 for Total AM Symptom Score (instantaneous).

C. Reviewer's Comments

The sponsor's multiple comparison procedure is somewhat unorthodox. The sponsor tested the 10 mg dose versus placebo and if that was significant, then tested all pairwise comparisons at the 0.05 level. This does control the per-experiment-wise error rate, but would be inadequate once the 10 mg dose was significant. Since the comparisons against placebo were highly significant ($P<0.01$) except for the 2.5 mg dose, the sponsor's conclusions are acceptable. [Any of the commonly used multiple comparison procedures, such as Dunnett's procedure, would declare these doses different from placebo.]

Given the failure of the 5 mg dose of DCL to show efficacy on Day 3 for the Total AM instantaneous assessment, the claim of onset on Day 2 based on the data from this study is somewhat problematic.

III. Phase III Studies

A. Study Description and Method of Analysis

These studies were similar to study C98-001 with the following exceptions:

1. Only the 5.0 mg and 7.5 mg doses of DCL were compared to placebo.
2. ~~Study C98-225 had a 4 week treatment period.~~
3. The sponsor also assessed cough.
4. To enter the study, the patient had to have, at the screening visit, the following reflective (prior 12 hours) sign/symptom scores as assessed jointly by the investigator and patient:
   a) A Nasal Rhinorrhea Symptom Score of at least 2 (moderate).
   b) A Total Nasal Symptom Score of at least 6.
   c) A Total Non-nasal Symptom Score of at least 5.

   At the time of randomization, for the three calendar days prior to baseline, the six bi-daily run-in reflective scores had to be the following:
   a) A Total Nasal Rhinorrhea score of at least 12.
   b) A Total Nasal score of at least 36.
   c) A Total Non-nasal score of at least 30.
5. To control experiment-wise error rate, the sponsor did a trend test using the treatment dose levels (0 for placebo). If this was significant, the sponsor did all pairwise comparisons at the 0.05 level.
6. The sample size was 450, 150 per treatment group.
7. The sponsor analyzed Total Symptom Scores both including and excluding cough. This review will only focus on the analysis excluding cough. (Note that the primary analysis is still Days 2-15, even for the four-week study C98-225.) [The Agency is of the opinion that cough is not a sign/symptom of seasonal allergic rhinitis.]

B. Results

1. Study C98-223

There were 496 patients (165 for DCL 5.0 mg, 166 for DCL 7.5 mg, and 165 placebo) randomized at 10 centers. A total of 18 patients (2 DCL 5.0 mg, 5 DCL 7.5 mg, and 11 placebo) failed to complete the study. Of these, 3 were for treatment failure (0 DCL 5.0 mg, 1 DCL 7.5 mg, and 2 placebo).

The treatment groups were comparable in demographic and baseline symptom severity.

Four patients (2 for DCL 7.5 mg and 2 placebo) were not included in the modified "intent-to-treat" analyses of the primary efficacy analysis because they failed to have both baseline and on-treatment diary assessments.

Table 2 provides the results of the analyses of Total Symptom Score (reflective) for combined AM/PM averages over Days 2-15, Total Nasal Symptom Score (reflective) for combined AM/PM averages over Days 2-15, and Total Symptom Score for AM [instantaneous (now) averages over Days 2-15 assessment]. The trend tests were significant for all 3 variables. The 5.0 mg dose of DCL showed efficacy for the primary efficacy variable, Total AM/PM Symptom Score (reflective). The 5.0 mg dose of DCL failed to show efficacy over placebo for Total Nasal AM/PM (reflective) and Total AM (now), although the P-value was 0.06 for both comparisons. The 7.5 mg dose was significant for all three variables.

Significance from placebo was seen in Total Symptom Score (both AM/PM reflective and AM instantaneous) on Day 3 for both DCL doses. Only the 7.5 mg dose of DCL was significantly different from placebo at Day 2 for Total AM/PM Symptom Score (reflective). The differences at Day 4 tended to be significant with the result of the Total AM instantaneous comparison being only nearly significant ($p=0.06$) at Day 4 for the 5.0 mg DCL versus placebo comparison.

2. Study C98-224

There were 492 patients (164 for DCL 5.0 mg, 164 for DCL 7.5 mg, and 164 placebo) randomized at 10 centers. A total of 25 patients (13 DCL 5.0 mg, 3 DCL 7.5 mg, and 9 placebo) failed to complete the study. Of these 11 were for treatment failure (7 DCL 5.0 mg, 0 DCL 7.5 mg, and 4 placebo).

The treatment groups were comparable in demographic and baseline symptom severity.

Three patients in the placebo group were not included in the modified "intent-to-treat" analyses of the primary efficacy analysis because they failed to have both baseline and on-treatment diary assessments.

Table 3 provides the results of the analyses of Total Symptom Score (reflective) for combined AM/PM averages over Days 2-15, Total Nasal Symptom Score (reflective) for combined AM/PM averages over Days 2-15, and Total Symptom Score for AM [Instantaneous (now) averages over Days 2-15 assessment]. The trend tests were significant for all 3 variables. The 7.5 mg dose of DCL failed to show efficacy over placebo for all three variables, whereas the 5.0 mg dose of DCL showed efficacy for all three variables.

No significant differences between either dose of DCL and placebo were seen for Total Symptom Score, both AM/PM reflective and AM instantaneous, on Days 2 and 3. (The DCL 5.0 mg versus placebo comparison had a p-value of 0.05 at Day 4 for the AM instantaneous assessment.)

3. Study C98-225

There were 475 patients (158 for DCL 5.0 mg, 159 for DCL 7.5 mg, and 158 placebo) randomized at 10 centers. A total of 37 patients (11 DCL 5.0 mg, 11 DCL 7.5 mg, and 15 placebo) failed to complete the study. Of these 15 were for treatment failure (5 DCL 5.0 mg, 3 DCL 7.5 mg, and 7 placebo).

The treatment groups were comparable in demographic and baseline symptom severity.

One 5.0 mg DCL patient was not included in the modified "intent-to-treat" analyses of the primary efficacy analysis because the patient failed to have both baseline and on-treatment diary assessments.

Table 4 provides the results of the analyses of Total Symptom Score (reflective) for combined AM/PM averages over Days 2-15, Total Nasal Symptom Score (reflective) for combined AM/PM averages over Days 2-15, and Total Symptom Score for AM [Instantaneous (now) averages over Days 2-15 assessment]. The trend tests were significant for all 3 variables. The 5.0 mg dose of DCL failed to show efficacy over placebo for all three variables whereas the 7.5 mg dose of DCL showed efficacy for two of the three variables.

Significance from placebo was seen in Total AM/PM Symptom Score (reflective) on Days 2 and 3, but not Day 4, for both doses of DCL. Significance from placebo was seen in Total AM Symptom Score (instantaneous) on Day 3 only for the 7.5 mg dose DCL.

C. Reviewer's Comments

The sponsor's multiple comparison procedure is somewhat unorthodox. The sponsor tested for an increasing trend of response on dose level and if that was significant, then tested all pairwise comparisons at the 0.05 level. This does control the per-experiment-wise error rate and is similar to the Fisher's protected lsd procedure. Since there are only three treatments, this procedure is adequate.

With the larger dose failing to show efficacy and the smaller dose showing efficacy in Study C98-224, one has to consider whether the study failed. Since the two dose levels studied are so close (differing by only 2.5 mg), such a result is not too anomalous. There is a large placebo response in all studies.

The results are somewhat inconsistent. The 5 mg dose of DCL failed to show efficacy in Study C98-225 whereas the 7.5 mg dose failed to show efficacy in Study C98-224. Both doses showed efficacy for the primary efficacy analysis in Study C98-233. Since the sponsor has provided two studies showing efficacy for both the 5.0 mg and 7.5 mg dose, the sponsor has provided adequate evidence of efficacy for both the 5.0 mg and 7.5 mg dose of DCL. [The efficacy of both doses in Study C98-001 is supportive.]

The results at early diary assessments were so variable that the sponsor's claim (that instantaneous assessments of efficacy at the end of the dosing interval demonstrated reductions in symptoms were observed following the first dose of desloratadine 5 mg and which were maintained for the full 24 hour dosing interval) is not adequately supported.

IV. Overall Comments

~~There were three phase III studies.~~ The results are somewhat inconsistent. The 5 mg dose of DCL failed to show efficacy in Study C98-225, whereas the 7.5 mg dose failed to show efficacy in Study C98-224. Both doses showed efficacy for the primary efficacy analysis, Total AM/PM combined reflective score averaged over Days 2-15, in Study C98-233. [Total Nasal AM/PM Nasal combined reflective score averaged over Days 2-15 was also significant or nearly significant, p=0.06 for the 5 mg dose.] The sponsor has, therefor, provided two studies demonstrating efficacy for the 5.0 mg and 7.5 mg dose of desloratadine for the primary efficacy variable, Total AM/PM Symptom Score (reflective over the last 12 hours). [The efficacy of both doses in Study C98-001 is supportive.] The results for Total AM instantaneous (now) Symptom Score are supportive of QD dose regimen.

The results at early diary assessments were so variable that the sponsor's claim that instantaneous assessments of efficacy at the end of the dosing interval demonstrated reductions in symptoms were observed following the first dose of desloratadine 5 mg and which were maintained for the full 24 hour dosing interval is not adequately supported.

/S/

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This review contains 8 pages of text and 2 pages of tables.

cc:
Archival NDA 21-165
HFD-570
HFD-570/Dr. Nicklas
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HFD-715/Div. File, Chron
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

Table 1

Least Squares mean changes, Mean % changes, and P-values for Days 2-15 Averages
Study C98-001

	DCL 2.5 mg QD (A)			DCL 5.0 mg QD (B)			DCL 7.5 mg QD (C)		
	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Total AM/PM (Prior 12 Hrs)	171	-3.2	(-20.0)	171	-4.3	(-28.0)	172	-4.3	(-26.7)
Total Nasal AM/PM (Prior 12 Hrs)	171	-1.6	(-17.3)	171	-2.2	(-27.1)	172	-2.3	(-25.2)
Total AM (Now)	171	-3.2	(-19.4)	169	-3.8	(-24.8)	171	-4.2	(-24.8)

	DCL 10 mg QD (D)			DCL 20mg QD (E)			Placebo		
	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Total AM/PM (Prior 12 Hrs)	170	-3.9	(-24.8)	169	-4.8	(-32.5)	173	-2.5	(-12.5)
Total Nasal AM/PM (Prior 12 Hrs)	170	-2.0	(-24.2)	169	-2.5	(-30.6)	173	-1.4	(-12.4)
Total AM (Now)	169	-3.8	(-23.7)	169	-4.4	(-29.8)	172	-2.4	(-12.0)

	P-values Compared to Placebo				
	A	B	C	D	E
Total AM/PM (Prior 12 Hrs)	0.19	<.01	<.01	<.01	<.01
Total Nasal AM/PM (Prior 12 Hrs)	0.40	<.01	<.01	0.01	<.01
Total AM (Now)	0.10	<.01	<.01	<.01	<.01

Table 2

Least Squares mean changes, Mean % changes, and P-values for Days 2-15 Averages
Study C98-223

	DCL 5 mg QD (A)			DCL 7.5 mg QD (B)			Placebo		
	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Total AM/PM (Prior 12 Hrs)	165	-4.56	(-27.8)	164	-5.22	(-30.9)	163	-3.52	(-21.7)
Total Nasal AM/PM (Prior 12 Hrs)	165	-2.27	(-24.9)	164	-2.67	(-29.3)	163	-1.80	(-20.4)
Total AM (Now)	165	-4.24	(-25.10	164	-4.62	(-27.4)	163	-3.29	(-19.5)

	P-values Compared to Placebo	
	A	B
Total AM/PM (Prior 12 Hrs)	0.03	<.01
Total Nasal AM/PM (Prior 12 Hrs)	0.06	<.01
Total AM (Now)	0.06	<.01

Table 3

Least Squares mean changes, Mean % changes, and P-values for Days 2-15 Averages
Study C98-224

	DCL 5 mg QD (A)			DCL 7.5 mg QD (B)			Placebo		
	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Total AM/PM (Prior 12 Hrs)	164	-5.06	(-30.2)	164	-4.08	(-23.9)	161	-3.85	(-21.7)
Total Nasal AM/PM (Prior 12 Hrs)	164	-2.58	(-28.1)	164	-2.15	(-22.8)	161	-1.97	(-20.8)
Total AM (Now)	164	-4.50	(-26.4)	164	-3.77	(-22.6)	161	-3.42	(-19.1)

	P-values Compared to Placebo	
	A	B
Total AM/PM (Prior 12 Hrs)	0.02	0.64
Total Nasal AM/PM (Prior 12 Hrs)	0.02	0.50
Total AM (Now)	0.03	0.48

Table 4

Least Squares mean changes, Mean % changes, and P-values for Days 2-15 Averages
Study C98-225

	DCL 5 mg QD (A)			DCL 7.5 mg QD (B)			Placebo		
	N	Mean	Mean % Change	N	Mean	Mean % Change	N	Mean	Mean % Change
Total AM/PM (Prior 12 Hrs)	157	-4.16	(-24.6)	159	-4.78	(-28.2)	158	-3.78	(-22.3)
Total Nasal AM/PM (Prior 12 Hrs)	157	-2.05	(-21.4)	159	-2.38	(-25.6)	158	-1.86	(-20.3)
Total AM (Now)	157	-3.56	(-20.7)	159	-4.46	(-26.2)	158	-3.55	(-20.7)

	P-values Compared to Placebo	
	A	B
Total AM/PM (Prior 12 Hrs)	0.41	0.03
Total Nasal AM/PM (Prior 12 Hrs)	0.44	0.03
Total AM (Now)	0.97	0.06